Traditional and Nontraditional Glycemic Markers and Risk of Peripheral Artery Disease: the Atherosclerosis Risk in Communities (ARIC) Study

by

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Abstract

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Introduction: Traditional glycemic markers, fasting glucose and hemoglobin A1c (HbA1c), predict incident peripheral artery disease (PAD). However, it is unknown whether nontraditional glycemic markers, fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG), have additional predictive value for PAD. Also, whether these glycemic markers demonstrate different associations with overall PAD and its severe form, critical limb ischemia (CLI), is yet to be evaluated.

Methods: We quantified the associations of these five glycemic markers with incident PAD (defined as hospitalizations with PAD diagnosis [ICD-9: 440.2-440.4] or leg revascularization [e.g., 38.18]) in 10,310 ARIC participants free of a history of PAD at baseline (1990-92) using Cox proportional hazards models. Of those with PAD, cases with an ICD code of ulcer, gangrene, or leg amputation were considered CLI. Participants were categorized into five groups according to the status of diabetes diagnosis and clinical cut-points of fasting glucose (<7.2, ≥7.2 mmol/L in diagnosed diabetes and <5.6, 5.6-6.9, ≥7.0 mmol/L in no diagnosed diabetes) and HbA1c (<7, ≥7% in diagnosed diabetes and <5.7, 5.7-6.4, and ≥6.5% in no diagnosed diabetes). The other glycemic markers were categorized according to percentiles corresponding to the HbA1c cut-points.

Results: Over a median follow-up of 18.4 years, there were 365 cases of PAD (126 were CLI). Both diagnosed diabetes and higher levels of HbA1c significantly contributed to increased risk of incident PAD (e.g., compared to no diagnosed diabetes with HbA1c <5.7%, the adjusted hazard ratio [HR] was 8.74 [95% confidence interval, 6.50-11.75] in

diagnosed diabetes with HbA1c ≥7% and 3.25 [2.14-4.93] in no diagnosed diabetes with HbA1c ≥6.5%). Fasting glucose showed weaker associations than HbA1c. The three nontraditional glycemic markers demonstrated similar risk gradient as HbA1c (e.g., adjusted HR ranged from 5.7-6.9 in diagnosed diabetes with higher levels vs. no diagnosed diabetes with lowest levels [lower and highest levels for 1,5-AG, respectively]), but once adjusting for HbA1c, their risk gradient was substantially attenuated. All glycemic markers, particularly HbA1c and the nontraditional glycemic markers, consistently demonstrated stronger associations with CLI (HRs ranging 12-21 in diagnosed diabetes with higher levels) than overall PAD (p for difference in HRs between CLI and PAD without CLI <0.001 in all glycemic markers).

Conclusions: Nontraditional glycemic markers provided similar predictive value as HbA1c for incident PAD but might not provide much additional information beyond HbA1c. Our results also support the importance of glucose metabolism in the progression to CLI.

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Background

Peripheral artery disease (PAD) is a condition characterized by atherosclerotic occlusive disease of the lower extremities [1], affecting approximately 8 to 12 million Americans [2, 3]. Approximately 1 of 5 patients with PAD die in 5 years [4, 5]. Critical limb ischemia (CLI) is a severe form of PAD [6], and 10% to 40% of patients with CLI require major amputation within 6 months after its diagnosis [2, 7]. Although amputation rates have recently decreased among patients with PAD over years [8], ~150,000 legs are still amputated due to PAD annually in the U.S. [9].

Although traditional atherosclerotic risk factors increase the risk of PAD, diabetes is known to be particularly strongly associated with PAD [10-12], with a relative risk of 3- to 4-fold compared to non-diabetes [13, 14]. Therefore, the American Diabetes Association (ADA) recommends annual foot care for patients with diabetes [15]. However, the adherence to this recommendation is reported to be ~30% [16, 17], and thus biomarkers that can classify the risk of PAD among diabetic patients may be helpful for targeted foot care.

In this context, traditional glycemic markers, fasting glucose and hemoglobin A1c (HbA1c), would be promising since they are routinely measured in patients with diabetes and predict PAD [18-22]. Although no studies have compared these two glycemic markers for PAD risk, previous studies have demonstrated the superiority of HbA1c to fasting glucose for predicting other cardiovascular outcomes and mortality [23-25]. However, HbA1c has a few caveats such as not reflecting recent changes in glucose levels and being influenced by red blood cell turnover (e.g., due to anemia) [26-30]. Also, it requires whole blood specimen to measure, often precluding its retrospective

measurement in a research setting, where only serum and/or plasma samples are typically stored.

Some nontraditional glycemic markers, fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG), may overcome these caveats of HbA1c, by reflecting glucose levels in the last few weeks, not being affected by red blood cell turn over, and being measurable in serum/plasma samples [31-35]. Recently, these nontraditional glycemic markers have been shown to predict coronary heart disease (CHD) and stroke similarly as HbA1c or provide additional predictive value beyond HbA1c [36, 37]. However, their associations with PAD risk have not been quantified.

Therefore, we comprehensively investigated the associations of traditional (fasting glucose and HbA1c) and nontraditional glycemic markers (fructosamine, glycated albumin, and 1,5-AG) with incident PAD in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. We also explored whether these glycemic markers have stronger relationships to incident CLI than incident PAD without CLI.

Method

Study Population

The ARIC Study enrolled 15,792 participants aged 45-64 years from four U.S. communities. The first clinic examinations (visit 1) took place from 1987 to 1989, with three short-term follow-up visits (visits 2-4) approximately every 3 years [38]. A total of 14,348 participants attended visit 2, which was the baseline of this study, given the data availability of the glycemic markers of interest. Of those participants, we excluded all

persons whose race/ethnicity was recorded as other than white or black (N = 42); who had missing variables of interest (N = 3,186); who were fasting <8 h (N = 347); or who had prevalent PAD at baseline (N = 463), leaving final sample of 10,310.

Measurement of Glycemic Markers

Serum glucose was measured using the hexokinase method. HbA1c was measured in whole blood samples using high-performance liquid chromatography with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2. Plus Glycohemoglobin and Tosoh G7 analyzers) [39]. Fructosamine (Roche Diagnostics Corp, Indianapolis, IN, USA), glycated albumin (Asashi Kasei Lucica GA-L, Tokyo, Japan), and 1,5-AG (GlycoMark, Winston-Salem, NC) were measured in 2012–2013 in stored serum samples from visit 2 (1990–1992) using a Roche Modular P800 system [36, 40]. Previous studies have shown these analytes to be reliable in long-term stored samples [41-46].

Other Variables of Interest at Baseline

Age, gender, race, educational level, alcohol use, and smoking status were self-reported. Body mass index (BMI) was calculated as body weight (in kilograms) over height (in meters) squared. Education was categorized as advanced (completed college or more), intermediate (high school to less than college), and no or basic (less than high school). Systolic blood pressure (SBP) was measured three times in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer, and the average of the second and third readings was recorded. Total cholesterol and high-density lipoprotein

(HDL) cholesterol were determined using enzymatic methods. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [47]. Medication use was verified by reviewing medication containers that participants brought to the visit. Diagnosed diabetes was defined as self-reported physician diagnosis of diabetes or current use of glucose lowering medications. History of CHD was defined by self-reported history of physician-diagnosed myocardial infarction, prior coronary reperfusion procedure, electrocardiogram evidence of myocardial infarction at visit 1, or adjudicated CHD events between visit 1 and visit 2 [48]. History of stroke was defined as a self-reported history of stroke at visit 1 or adjudicated stroke events between visit 1 and visit 2.

Incident Peripheral Artery Disease

Based on previous literature [21,22], incident PAD was defined as hospitalizations with the following International Classification of Diseases (ICD) codes: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, cases based on 440.22, 440.23, and 440.24 as well as PAD cases with coexisting leg amputation (84.1x), lower extremity ulcer (707.1x), and

gangrene (785.4) were considered CLI. Participants were followed until incident PAD, date of death, date of the last contact, or December 31, 2012, whichever came first.

Statistical Analyses

We first categorized participants into five groups according to the status of diagnosed diabetes and levels of traditional glycemic markers. We used clinical cut-points recommended by the ADA to categorize fasting glucose and HbA1c [49]. Specifically, fasting glucose levels were categorized into <5.6, 5.6-6.9, and ≥7 mmol/L in no diagnosed diabetes and <7.2, ≥7.2 mmol/L in diagnosed diabetes. Similarly, HbA1c were categorized into <5.7, 5.7-6.4, and ≥6.5% in no diagnosed diabetes and <7, ≥7% in diagnosed diabetes. We subsequently categorized participants into five groups by the status of diagnosed diabetes and percentiles of for nontraditional glycemic markers corresponding to HbA1c cut-points since their clinical cut-points are not established. In persons with no diagnosed diabetes, HbA1c values of 5.7% and 6.5% corresponded to the 77th percentile and the 96th percentile, respectively. In persons with diagnosed diabetes, HbA1c of 7% was equivalent to the 32nd percentile. The cut-points for 1,5-AG were inversed (e.g., 23rd percentile instead of 77th percentile) because its lower values indicate hyperglycemia [50].

Baseline characteristics of the study population were compared between participants with and without incident PAD during follow-up. We used Poisson regression models with linear splines to evaluate the continuous association between the glycemic markers and incidence rate of PAD with the adjustment of age, sex and race. Cox proportional hazards models were used to quantify the independent associations between categories of

glycemic markers and incident PAD beyond potential confounders. We constructed three models for the adjustment of covariates. Model 1 was adjusted for key demographic and clinical factors, age (years), race, sex, education level, BMI, total cholesterol, HDL cholesterol, drinking status (current, former, never), smoking status (current, former, never), SBP, antihypertensive medication use, lipid lowering medication use, estimated glomerular filtration rate (eGFR), history of CHD and stroke. Model 2 was additionally adjusted for each of traditional glycemic markers (Model 2a with fasting glucose and Model 2b with HbA1c). We primarily used the category with no diagnosed diabetes and the lowest level of glycemic markers (highest for 1,5-AG but for convenience we would not specify every time in subsequent sections) as a reference but secondarily repeated the analysis with the lowest risk group as a reference group in a case of a J-shaped association. The proportional hazards assumption was verified using log-log plots. Seemingly unrelated regression was used to formally compare the strength of associations for each glycemic marker with incident PAD without CLI vs. CLI.

All statistical analyses were conducted using Stata SE, version 14 (Stata Corp, College Station, TX), and a p value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of participants by the status of incident PAD during follow-up are shown in Table 1. Compared to participants who did not developed PAD, those who developed PAD were more likely to be older, male, black race, less educated, current smoker, and to have poorer risk factor profile (i.e., higher levels of BMI and SBP,

lower eGFR, and higher prevalence of lipid lowering medication use and a history of CHD and stroke). Regarding diagnosed diabetic status and glycemic markers, participants with incident PAD had ~4-fold higher prevalence of diagnosed diabetes and higher levels of all glycemic markers (lower levels of 1,5-AG) than those without incident PAD. These patterns were more enhanced in in persons who developed CLI compared with those who developed PAD without CLI. More than half of persons who developed CLI had diagnosed diabetes at baseline.

Over a median follow-up of 18.4 years, there were 365 cases of PAD (126 were CLI). The overall incidence rate of PAD was 1.9 per 1,000 person-years. The continuous associations of five glycemic markers with incidence rate of PAD adjusted for age, sex, and race are shown in Figure 1. The incidence rate of PAD increased monotonically along with both traditional glycemic markers, although the risk gradient appeared to be steeper for HbA1c (e.g., reaching incidence rate of 20 per 1,000 person-years at 99th percentile in Figure 1B) than fasting glucose (e.g., incidence rate at 99th percentile <15 per 1,000 person-years in Figure 1A). The nontraditional glycemic markers were associated with increased incidence rate of PAD as well but demonstrated J-shaped associations, although less so for 1,5-AG. Their risk gradients appeared to be slightly shallower than HbA1c but steeper than fasting glucose (incidence rate at 99th percentile exceeding 15 per 1,000 person-years in Figures 1C-E).

After accounting for other potential confounders, both traditional glycemic markers showed significant associations with incident PAD (Model 1 in Table 2). Again, the associations were stronger for HbA1c than for fasting glucose. Specifically, the adjusted hazard ratio (HR) in diagnosed diabetes with HbA1c ≥7% (vs. no diagnosed

diabetes with HbA1c <5.7%) was 8.74 (95% confidence interval, 6.50-11.75), whereas that in diagnosed diabetes with fasting glucose ≥7.2 mmol/L (vs. no diagnosed diabetes with fasting glucose <5.6 mmol/L) was 5.65 (4.11-7.76). In addition, higher HbA1c levels, but not fasting glucose levels, were significantly associated with incident PAD among no diagnosed diabetes. Persons with prediabetes, indicated by a HbA1c concentration of 5.7-6.4%, had ~50% higher risk of PAD compared to those with HbA1c <5.7%. The additional adjustment for fasting glucose somewhat attenuated the associations for HbA1c (Model 2a in Table 2), but the general patterns remained consistent. On the other hand, there was no longer a risk gradient by fasting glucose levels among those with diagnosed diabetes after the additional adjustment for HbA1c, with both groups showing HR ~2 (Model 2b in Table 2).

Regardless of traditional glycemic markers, adjusted HRs were generally higher for CLI than for PAD, particularly in persons with diagnosed diabetes. For example, the adjusted HR for CLI in diagnosed diabetes with HbA1c ≥7% (vs. no diagnosed diabetes with HbA1c <5.7%) was 20.78 (12.51-34.50) in Model 1 and 11.55 (5.97-22.36) in Model 2a. Based on seemingly unrelated regression, HRs for both traditional glycemic markers were significantly greater for CLI than for PAD without CLI (p values <0.001 for both markers).

The associations of nontraditional glycemic markers with incident PAD were independent of representative cardiovascular risk factors as well (Model 1 in Table 3). The adjusted HRs appeared to be slightly smaller than those for HbA1c but greater than those for fasting glucose. Specifically, the adjusted HRs in diagnosed diabetes with their higher category (vs. no diagnosed diabetes with their lowest category) ranged from 5.7 to

6.9. Given a J-shaped association for fructosamine and 1,5-AG, when their lowest risk category was used as a reference, the corresponding HRs exceeded 7.5 (Web Table 1). Unlike fasting glucose, the adjusted HRs in no diagnosed diabetes with their highest category reached statistical significance. The further adjustment for fasting glucose attenuated the associations, but the general patterns remained similar (Model 2a in Table 3). However, when we replaced fasting glucose with HbA1c, the risk gradient within no diagnosed diabetes and diagnosed diabetes was not that evident in any of the nontraditional glycemic markers.

Consistently with both traditional glycemic markers, all three nontraditional glycemic markers showed greater HRs for CLI than for overall PAD, with HRs adjusted for conventional cardiovascular factors ranging from 12 to 17 in diagnosed diabetes with higher levels and 3 to 5 in diagnosed diabetes with lower levels (vs. no diagnosed diabetes with the lowest levels) (Model 1 in Table 3). Those HRs for CLI were significantly greater than those for PAD without CLI in seemingly unrelated regression analyses (p for difference <0.001 for all nontraditional glycemic markers).

Discussion

In this community-based study, both traditional (fasting glucose and HbA1c) and nontraditional (fructosamine, glycated albumin, and 1,5-AG) glycemic markers were significantly associated with incident PAD, independently of potential confounders. The association with incident PAD was particularly strong and robust when persons with and without diagnosed diabetes were categorized by HbA1c. Overall, nontraditional glycemic markers demonstrated strength of association with PAD in the middle of HbA1c and

fasting glucose. Of note, all glycemic markers tested consistently demonstrated stronger associations with CLI than overall PAD.

The independent associations of traditional glycemic markers with PAD were consistent with previous reports mainly among diabetic patients [18-22, 51-54], but our study extended our knowledge in a few aspects. First, we confirmed these associations in the general population (particularly for HbA1c). Specifically, we found persons with prediabetes, indicated by a HbA1c concentration 5.7-6.4%, had ~50% higher risk of PAD compared to those with HbA1c <5.7%. Second, HbA1c demonstrated stronger associations with PAD compared to fasting glucose levels, confirming the pattern observed for other cardiovascular outcomes and mortality [23-25]. Third, both traditional glycemic markers demonstrated stronger associations with CLI than overall PAD. Fourth, while most previous studies were cross-sectional [51-54] or had relatively short duration of follow-up (a median of ≤6 years) [19-21], our study explored a long follow-up of over 22 years.

To our knowledge, this is the first study reporting the associations of three nontraditional glycemic markers, fructosamine, glycated albumin, and 1,5-AG, with incident PAD, independent of traditional cardiovascular risk factors. Their associations with PAD were not as strong as but similar to HbA1c. Once accounting for HbA1c, their predictive values for PAD were considerably attenuated. These patterns are generally consistent with previous reports from ARIC for other cardiovascular diseases (CHD, stroke, and heart failure) [36, 37].

In our study, we found J-shaped associations of the levels of nontraditional glycemic markers (particularly fructosamine in both Figure 1 and Table 3) with incident

PAD. Of interest, low levels of fructosamine have been reported to be associated with increased risk of mortality [37, 55] and heart failure [37]. Several mechanisms might partly explain these associations. Fructosamine values are lower among those with low concentration of serum albumin (hypoalbuminemia below 30-35 g/L), as in the case of protein-losing enteropathy, nephrotic syndrome, and advanced liver disease like cirrhosis. Increased albumin catabolism also leads to low fructosamine levels in hyperthyroidism, glucocorticoid administration, and Cushing's syndrome [56-59]. Therefore, the lowest category of fructosamine might include individuals with poor health and low serum albumin levels, who were at high risk of PAD. This mechanism of increased albumin catabolism also results in low glycated albumin levels, which may be related to a J-shaped association between glycated albumin and PAD risk.

Although PAD is often considered as a large artery disease, microvascular disease is indicated to play an important factor in the development of CLI, by impairing collateral formation and wound healing [60, 61]. Our observation of all five glycemic markers consistently demonstrating stronger associations with CLI than overall PAD seems to support the involvement of microvascular disease in the pathophysiology of CLI, since hyperglycemia is known to be more strongly associated with microvascular disease (namely retinopathy, nephropathy, and neuropathy) than macrovascular disease (e.g., CHD) in general [62]. In addition, an intensive glycemic control decreases the risk of microvascular disease but not necessarily macrovascular disease in patients with diabetes [63, 64]. Nonetheless, future studies should explore other parameters of microvascular disease (e.g., retinopathy) and their associations with CLI vs. overall PAD.

Our results have several clinical and research implications. First, HbA1c, the

central glycemic marker for glucose control in diabetic patients, would be useful for classifying the risk of PAD. Given the low adherence to annual foot care among diabetic patients recommended by the ADA, HbA1c may be used to identify diabetic patients who would particularly benefit from foot care and monitoring. Second, although an intensive glucose control has not consistently shown an evident benefit for reducing overall cardiovascular risk, our results suggest that such a tight control may contribute to the reduction of CLI. Third, although the three nontraditional glycemic markers did not outperform HbA1c for predicting incident PAD, there may be a few scenarios that these markers may be useful, since they showed stronger associations than fasting glucose. For example, fructosamine and glycated albumin can be measured rapidly, easily, precisely, and inexpensively [65]. Therefore, these nontraditional glycemic markers may be used in clinical practice or research setting with limited resources (e.g., developing countries [66]). In addition, these nontraditional glycemic markers can be assessed with serum and plasma samples, while HbA1c requires the whole blood sample. Therefore, when research studies or trials have only stored serum or plasma, these nontraditional glycemic markers would be reasonable alternatives as useful glycemic markers and potent predictors for PAD.

There are several limitations in our study. First, glycemic markers were based on single measurement at baseline. Second, the definition of PAD (and CLI) relied on discharge diagnostic codes. Thus, asymptomatic cases and mild cases were unlikely to be captured. However, it is important to study severe PAD, since revascularization procedures and inpatient care account for majority of medical expenditure related to PAD (e.g., $3.9 billion for total Medicare paid PAD-related care annually) [67, 68]. Third, we

are not able to eliminate the possibility of residual confounding, as is the case in any observation studies. Finally, we investigated whites and blacks aged 47-70 years, so the results may not be generalizable to other racial or age groups.

In conclusion, traditional (particularly HbA1c) and nontraditional glycemic markers were strongly associated with incident PAD, independently of potential confounders. Additional prognostic values of nontraditional glycemic markers beyond HbA1c for PAD were not evident. Nonetheless, all five glycemic markers demonstrated stronger associations with CLI than overall PAD. These results suggest the usefulness of HbA1c and nontraditional glycemic markers to identify persons (particularly with diabetes) at high risk of PAD and the importance of hyperglycemia in the progression to CLI.

Tables and figures

Table 1. Baseline Characteristics by Categories of PAD during Follow-up (N=10,310)

Characteristic	Overall	No PAD	PAD		
			All	PAD without CLI	CLI
n	10,310	9,945	365	239	126
Age, years	57.0 (5.7)	56.9 (5.7)	58.8 (5.5)	58.9 (5.4)	58.5 (5.7)
Female, %	58.5	59.0	46.0	41.4	54.8
Black, %	22.7	22.5	27.1	17.2	46.0
Body mass index, kg/m^2	28.0 (5.4)	28.0 (5.4)	29.0 (5.4)	28.2 (4.9)	30.5 (6.0)
Education level, %					
No or basic	20.3	19.9	31.2	26.4	40.5
Intermediate	41.9	42.1	38.6	39.3	37.3
Advanced	37.7	38.0	30.1	34.3	22.2
Smoking status, %					
Current smoker, %	20.4	19.8	34.8	38.5	27.8
Former smoker, %	38.6	38.7	37.5	39.3	34.1
Drinking status, %					
Current drinker, %	56.9	57.0	53.4	61.9	37.3
Former drinker, %	20.6	20.4	26.3	23.0	32.5
Diagnosed diabetes, %	8.3	7.4	31.0	19.2	53.2
Blood glucose, mmol/L	6.27 (2.21)	6.20 (2.07)	8.16 (4.22)	7.13 (3.22)	10.10 (5.14)
HbA1c, %	5.75 (1.17)	5.71 (1.10)	6.89 (2.19)	6.27 (1.51)	8.06 (2.74)
Fructosamine, µmol/L	238.40 (47.96)	237.00 (44.88)	276.58 (92.72)	251.48 (63.67)	324.18 (117.58)
Glycated albumin, %	13.55 (3.76)	13.44 (3.49)	16.69 (7.53)	14.46 (4.83)	20.90 (9.67)
1,5-Anhydroglucitol, ug/ml	17.63 (6.61)	17.75 (6.47)	14.54 (9.23)	16.49 (8.34)	10.83 (9.71)
Systolic blood pressure, mmHg	121.3 (18.5)	121.0 (18.3)	129.4 (21.9)	128.0 (20.9)	132.1 (23.5)
Total cholesterol, mmol/L	5.43 (1.02)	5.42 (1.01)	5.62 (1.10)	5.58 (1.06)	5.68 (1.18)

HDL cholesterol, mmol/L	1.30 (0.44)	1.30 (0.44)	1.10 (0.35)	1.10 (0.36)	1.09 (0.32)
eGFR, ml/min	96.3 (15.5)	96.5 (15.1)	90.7 (23.1)	90.1 (19.3)	91.9 (29.0)
Antihypertensive medication, %	36.4	35.5	60.8	57.3	67.5
Lipid lowering medication, %	7.1	6.9	13.2	13.4	12.7
History of coronary heart disease, %	6.0	5.4	20.5	23.0	15.9
History of stroke, %	1.8	1.7	4.7	4.6	4.8

Table 2. Adjusted HRs (95% CIs) for peripheral artery disease and critical limb ischemia by categories of fasting glucose and HbA1c (N = 10,310)

	Peripheral artery disease n=365			**Critical limb ischemia n=126**		
	Model 1	Model 2a	Model 2b	Model 1	Model 2a	Model 2b
Fasting glucose						
No diagnosis of diabetes						
<5.6 mmol/L	1 (reference)		1 (reference)	1 (reference)		1 (reference)
5.6-6.9 mmol/L	1.02 (0.77, 1.34)		0.96 (0.73, 1.26)	0.95 (0.54, 1.68)		0.87 (0.49, 1.54)
≥7.0 mmol/L	1.49 (0.96, 2.31)		0.86 (0.54, 1.39)	1.51 (0.65, 3.50)		0.70 (0.29, 1.73)
Diagnosis of diabetes						
<7.2 mmol/L	**2.79 (1.54, 5.04)**		**2.09 (1.15, 3.80)**	**3.40 (1.15, 10.07)**		2.32 (0.77, 6.94)
≥7.2 mmol/L	**5.65 (4.11, 7.76)**		**1.75 (1.12, 2.74)**	**12.25 (7.08, 21.19)**		**2.74 (1.31, 5.71)**
HbA1c						
No diagnosis of diabetes						
HbA1c <5.7%	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
HbA1c 5.7-6.4%	**1.47 (1.09, 1.97)**	**1.43 (1.06, 1.92)**		1.58 (0.86, 2.91)	1.54 (0.84, 2.83)	
HbA1c ≥6.5%	**3.25 (2.14, 4.93)**	**2.66 (1.71, 4.16)**		**4.10 (1.96, 8.56)**	**3.14 (1.46, 6.77)**	
Diagnosis of diabetes						
HbA1c <7.0%	**2.33 (1.38, 3.94)**	**2.09 (1.23, 3.55)**		**4.14 (1.70, 10.10)**	**3.55 (1.45, 8.73)**	
HbA1c ≥7.0%	**8.74 (6.50, 11.75)**	**5.73 (3.74, 8.79)**		**20.78 (12.51, 34.50)**	**11.55 (5.97, 22.36)**	

Model 1 was adjusted for age (years), race (black, white), sex (male, female), education level, body mass index, total cholesterol, high-density lipoprotein cholesterol, drinking status (current, former, never), smoking status (current, former, never), systolic blood pressure, blood pressure–lowering medication use, cholesterol–lowering medication use, estimated glomerular filtration rate, history of coronary artery disease and stroke. Model 2a was adjusted for all variables in model 1 and fasting glucose. Model 2b was adjusted for all variables in model 1 and HbA1c.

Table 3. Adjusted HRs (95% CIs) for peripheral artery disease and critical limb ischemia by categories of fructosamine, glycated albumin, and 1,5-AG (N = 10,310)

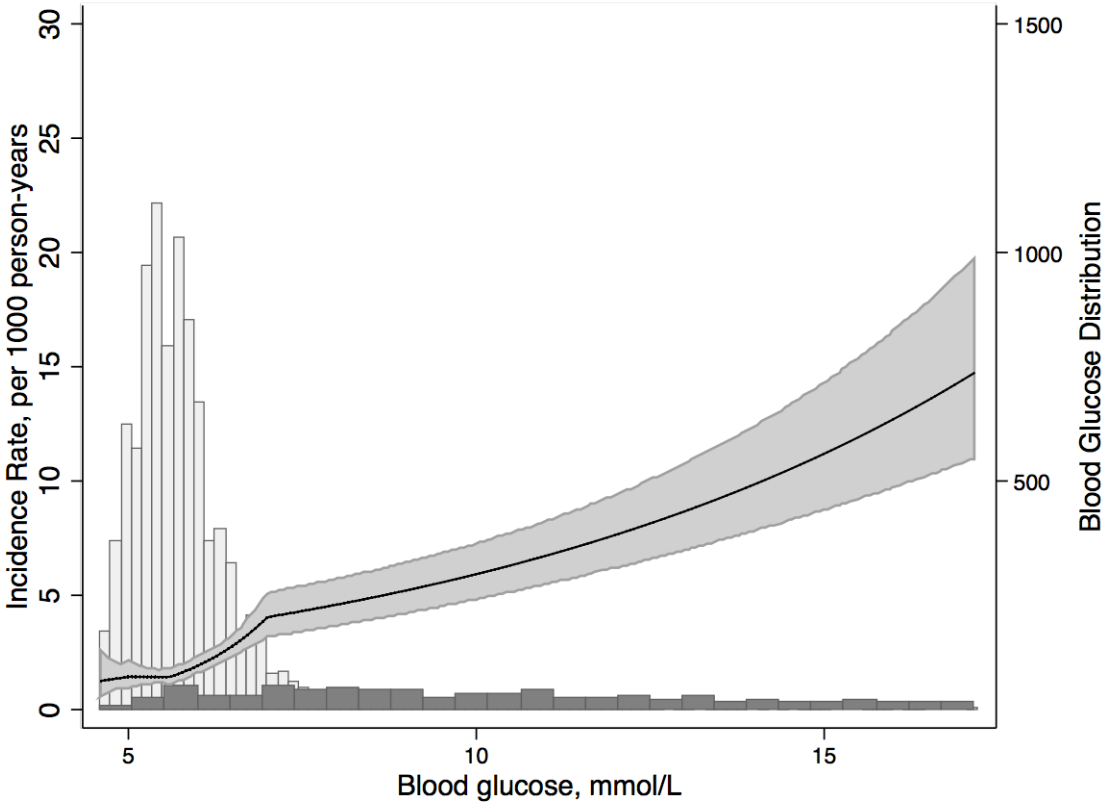
	Peripheral artery disease n=365			**Critical limb ischemia n=126**		
	Model 1	Model 2a	Model 2b	Model 1	Model 2a	Model 2b
Fructosamine						
No diagnosis of diabetes						
<77th Percentile (<241.5 µmol/L)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
77th-95th Percentile (241.5 - 270.0 µmol/L)	0.72 (0.50, 1.04)	0.69 (0.48, 0.99)	0.68 (0.47, 0.97)	0.44 (0.19, 1.06)	0.43 (0.18, 1.02)	0.41 (0.17, 0.97)
≥96th Percentile (≥270.1 µmol/L)	**1.73 (1.09, 2.73)**	1.21 (0.74, 1.98)	0.93 (0.56, 1.54)	**2.58 (1.25, 5.32)**	1.76 (0.82, 3.77)	1.14 (0.51, 2.53)
Diagnosis of diabetes						
<32nd Percentile (<275.3 µmol/L)	**2.86 (1.85, 4.41)**	**2.42 (1.56, 3.76)**	**2.09 (1.34, 3.25)**	**5.50 (2.79, 10.83)**	**4.60 (2.32, 9.13)**	**3.64 (1.82, 7.28)**
≥32nd Percentile (≥275.3 µmol/L)	**5.72 (4.30, 7.60)**	**2.73 (1.77, 4.21)**	**1.62 (1.03, 2.54)**	**12.30 (7.82, 19.37)**	**5.52 (2.94, 10.37)**	**2.60 (1.31, 5.15)**
Glycated albumin						
No diagnosis of diabetes						
<77th Percentile (<13.6%)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
77th-95th Percentile (13.6 - 15.5%)	1.09 (0.77, 1.55)	1.06 (0.75, 1.50)	1.01 (0.71, 1.43)	1.10 (0.54, 2.24)	1.08 (0.53, 2.20)	1.01 (0.50, 2.07)
≥96th Percentile (≥15.6%)	**2.45 (1.58, 3.79)**	**1.83 (1.14, 2.95)**	1.34 (0.82, 2.18)	**4.69 (2.38, 9.26)**	**3.50 (1.71, 7.20)**	**2.26 (1.06, 4.82)**
Diagnosis of diabetes						

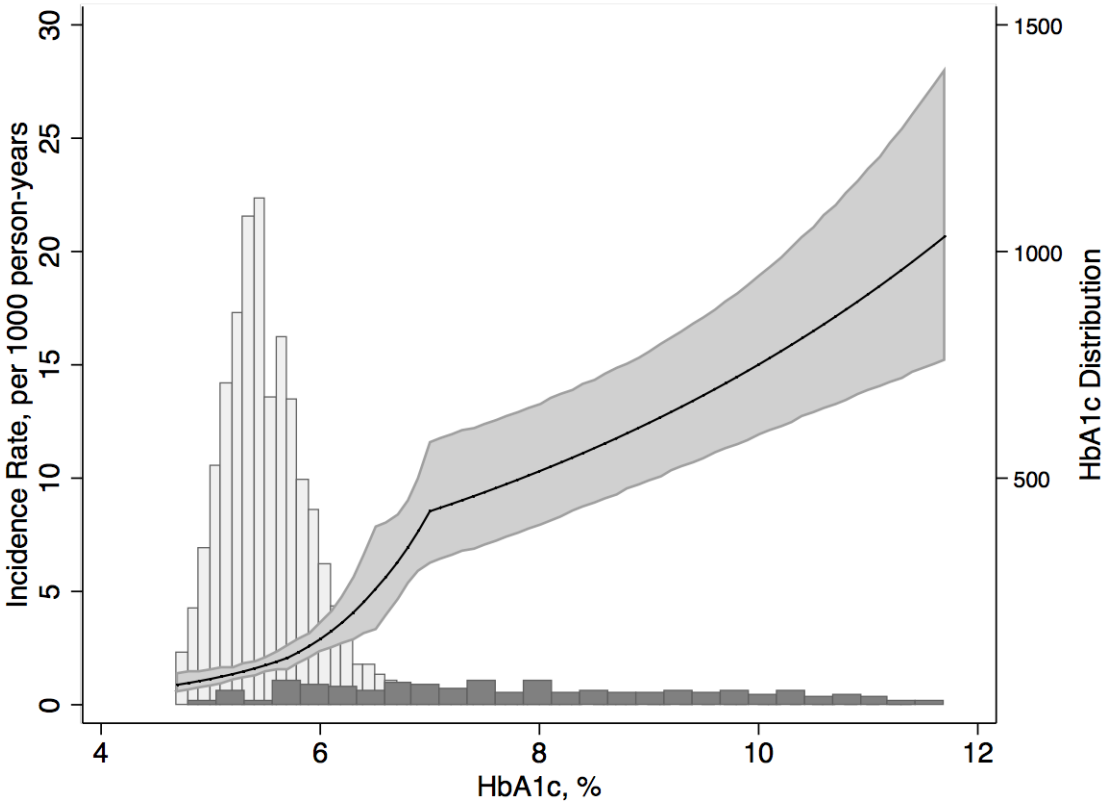
<32nd Percentile (<16.4%)	**2.51 (1.57, 4.02)**	**2.22 (1.38, 3.57)**	**1.95 (1.21, 3.14)**	**4.75 (2.19, 10.33)**	**4.21 (1.93, 9.20)**	**3.51 (1.60, 7.70)**
≥32nd Percentile (≥16.4%)	**6.90 (5.21, 9.13)**	**3.98 (2.60, 6.08)**	**2.30 (1.47, 3.59)**	**17.32 (10.89, 27.55)**	**9.78 (5.23, 18.27)**	**4.74 (2.41, 9.32)**
1,5-AG						
No diagnosis of diabetes						
>23rd Percentile (>14.6 ug/ml)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
5th-23rd Percentile (7.9 - 14.6 ug/ml)	0.90 (0.64, 1.27)	0.89 (0.63, 1.26)	0.88 (0.63, 1.24)	0.69 (0.32, 1.47)	0.69 (0.32, 1.47)	0.68 (0.32, 1.45)
≤4th Percentile (≤7.8 ug/ml)	**1.90 (1.18, 3.05)**	1.50 (0.91, 2.47)	1.17 (0.70, 1.96)	**2.81 (1.26, 6.27)**	2.09 (0.90, 4.87)	1.35 (0.56, 3.28)
Diagnosis of diabetes						
>68th Percentile (>9.7 ug/ml)	**1.95 (1.18, 3.23)**	**1.68 (1.01, 2.81)**	1.50 (0.90, 2.50)	**3.18 (1.41, 7.14)**	**2.72 (1.20, 6.16)**	2.26 (0.99, 5.13)
≤68th Percentile (≤9.7 ug/ml)	**6.74 (5.13, 8.86)**	**3.99 (2.66, 5.98)**	**2.41 (1.57, 3.71)**	**14.73 (9.54, 22.76)**	**8.27 (4.54, 15.06)**	**3.97 (2.05, 7.69)**

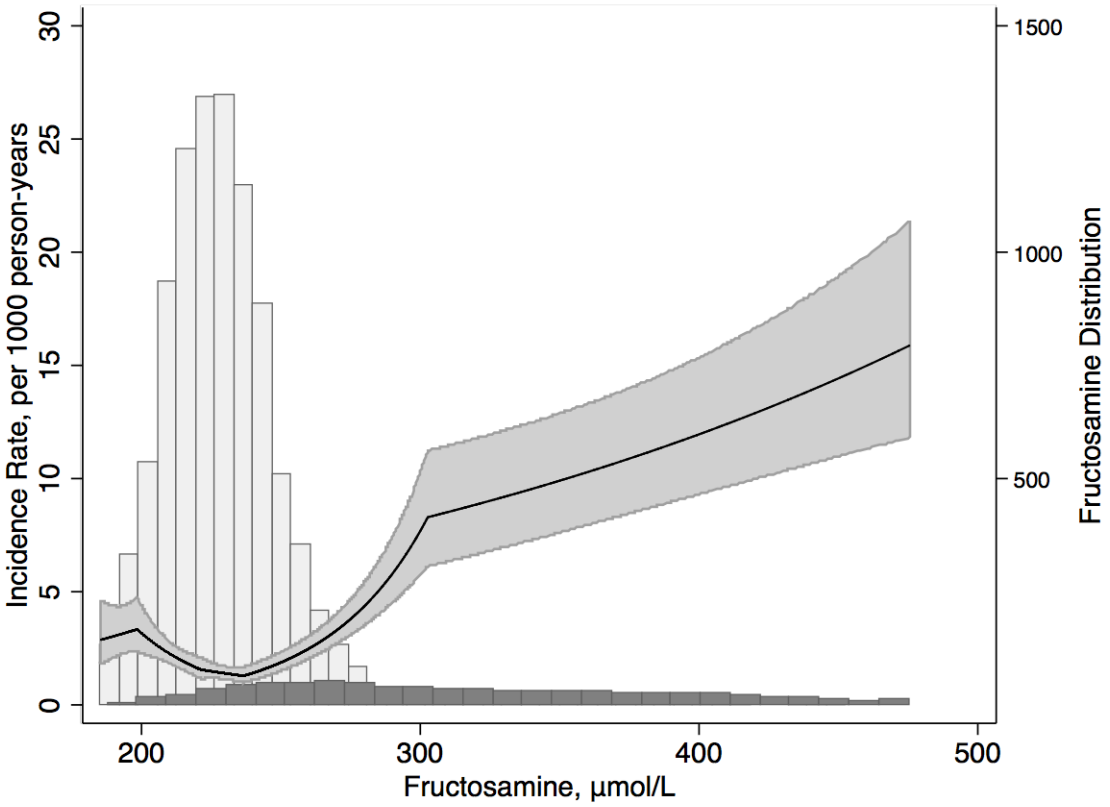
Models are the same as Table 2.

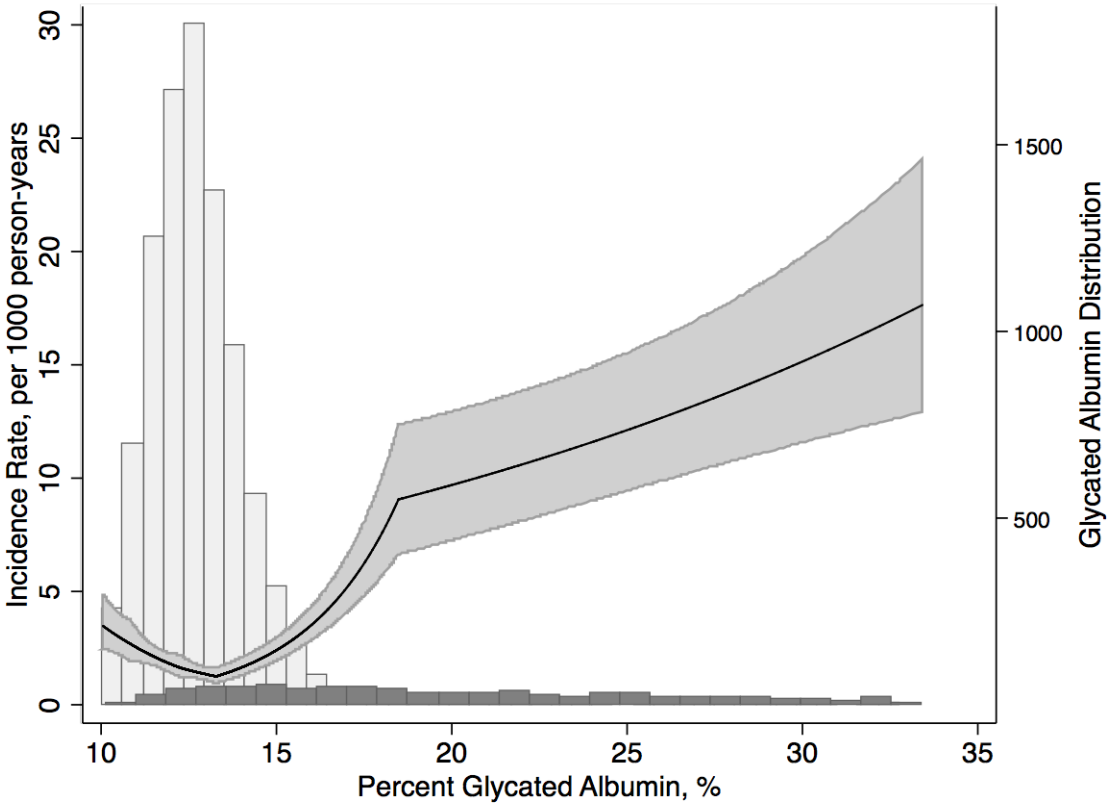
Figure 1. Adjusted incidence rates of peripheral artery disease by (A) fasting blood glucose, (B) HbA1c, (C) fructosamine, (D) glycated albumin, and (E) 1,5-AG.

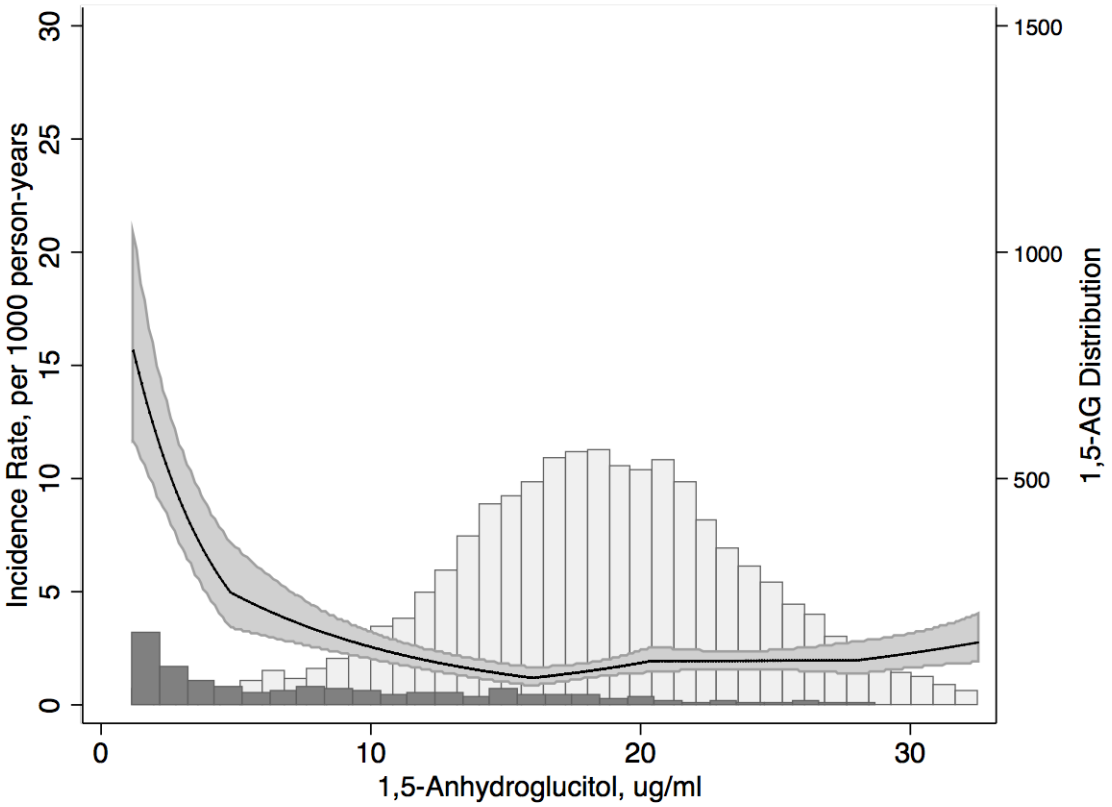
The graph shows incidence rate per 1,000 person-years and 95% CIs (shaded area) of PAD with spline terms of A1c (knots at 5.7, 6.5, and 7%), fasting glucose (knots at 5.0, 5.6, and 7mmol/l), fructosamine, glycated albumin, and 1,5-AG (knots at the 5th, 35th, 65th, and 95th percentiles) adjusted for age, race, and sex; trimmed at 1% and 99%. Frequency histograms were shown for persons without diabetes (gray bars) and for persons with diabetes (black bars).




Incidence Rate, per 1000 person-years
0
5
10
15
20
25
30
4
6
8
10
12
HbA1c, %
1500
1000
500
HbA1c Distribution


Incidence Rate, per 1000 person-years
0
5
10
15
20
25
30
200
300
400
500
Fructosamine, µmol/L
1500
1000
500
Fructosamine Distribution


Incidence Rate, per 1000 person-years
0
5
10
15
20
25
30
10
15
20
25
30
35
Percent Glycated Albumin, %
500
1000
1500
Glycated Albumin Distribution


Incidence Rate, per 1000 person-years
0
5
10
15
20
25
30
0
10
20
30
1,5-Anhydroglucitol, ug/ml
500
1000
1500
1,5-AG Distribution

Appendix

Web Table 1. Adjusted HRs (95% CIs) for peripheral artery disease and critical limb ischemia by categories of fructosamine, glycated albumin, and 1,5-AG (N = 10,310) (lowest risk group as reference)

	Peripheral artery disease n=365			**Critical limb ischemia n=126**		
	Model 1	Model 2a	Model 2b	Model 1	Model 2a	Model 2b
Fructosamine						
No diagnosis of diabetes						
<77th Percentile (<241.5 µmol/L)	1.39 (0.97, 2.00)	**1.45 (1.01, 2.09)**	**1.48 (1.03, 2.13)**	2.26 (0.95, 5.39)	2.35 (0.99, 5.61)	**2.46 (1.03, 5.86)**
77th-95th Percentile (241.5 - 270.0 µmol/L)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥96th Percentile (≥270.1 µmol/L)	**2.40 (1.40, 4.09)**	**1.75 (1.00, 3.07)**	1.37 (0.77, 2.43)	**5.82 (2.09, 16.22)**	**4.13 (1.44, 11.82)**	2.80 (0.96, 8.21)
Diagnosis of diabetes						
<32nd Percentile (<275.3 µmol/L)	**3.97 (2.34, 6.73)**	**3.51 (2.06, 5.97)**	**3.09 (1.81, 5.25)**	**12.41 (4.49, 34.28)**	**10.82 (3.90, 29.99)**	**8.94 (3.22, 24.82)**
≥32nd Percentile (≥275.3 µmol/L)	**7.94 (5.32, 11.84)**	**3.96 (2.39, 6.55)**	**2.39 (1.42, 4.01)**	**27.77 (11.73, 65.75)**	**12.98 (4.98, 33.81)**	**6.39 (2.38, 17.13)**
Glycated albumin						
No diagnosis of diabetes						
<77th Percentile (<13.6%)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
77th-95th Percentile (13.6 - 15.5%)	1.09 (0.77, 1.55)	1.06 (0.75, 1.50)	1.01 (0.71, 1.43)	1.10 (0.54, 2.24)	1.08 (0.53, 2.20)	1.01 (0.50, 2.07)
≥96th Percentile (≥15.6%)	**2.45 (1.58, 3.79)**	**1.83 (1.14, 2.95)**	1.34 (0.82, 2.18)	**4.69 (2.38, 9.26)**	**3.50 (1.71, 7.20)**	**2.26 (1.06, 4.82)**
Diagnosis of diabetes						
<32nd Percentile (<16.4%)	**2.51 (1.57, 4.02)**	**2.22 (1.38, 3.57)**	**1.95 (1.21, 3.14)**	**4.75 (2.19, 10.33)**	**4.21 (1.93, 9.20)**	**3.51 (1.60, 7.70)**
≥32nd Percentile (≥16.4%)	**6.90 (5.21, 9.13)**	**3.98 (2.60, 6.08)**	**2.30 (1.47, 3.59)**	**17.32 (10.89, 27.55)**	**9.78 (5.23, 18.27)**	**4.74 (2.41, 9.32)**

1,5-AG						
No diagnosis of diabetes						
>23rd Percentile (>14.6 ug/ml)	1.11 (0.79, 1.56)	1.12 (0.80, 1.58)	1.13 (0.80, 1.59)	1.46 (0.68, 3.13)	1.46 (0.68, 3.12)	1.47 (0.69, 3.15)
5th-23rd Percentile (7.9 - 14.6 ug/ml)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≤4th Percentile (≤7.8 ug/ml)	**2.11 (1.22, 3.64)**	1.68 (0.95, 2.96)	1.32 (0.74, 2.36)	**4.10 (1.48, 11.36)**	**3.04 (1.06, 8.71)**	1.99 (0.67, 5.88)
Diagnosis of diabetes						
>68th Percentile (>9.7 ug/ml)	**2.16 (1.22, 3.83)**	**1.89 (1.06, 3.37)**	1.69 (0.95, 3.02)	**4.63 (1.66, 12.93)**	**3.96 (1.41, 11.11)**	**3.32 (1.18, 9.33)**
≤68th Percentile (≤9.7 ug/ml)	**7.47 (5.08, 10.98)**	**4.47 (2.76, 7.25)**	**2.73 (1.65, 4.50)**	**21.49 (10.03, 46.06)**	**12.03 (5.06, 28.59)**	**5.84 (2.37, 14.39)**

Models are the same as Table 2.

Web Table 2. Adjusted HRs (95% CIs) for peripheral artery disease without critical limb ischemia by categories of fasting glucose and HbA1c (N = 10,310)

	PAD without CLI n=239		
	Model 1	Model 2a	Model 2b
Fasting glucose			
No diagnosis of diabetes			
<5.6 mmol/L	1 (reference)		1 (reference)
5.6-6.9 mmol/L	1.05 (0.77, 1.43)		1.00 (0.73, 1.37)
≥7.0 mmol/L	1.55 (0.93, 2.60)		1.08 (0.61, 1.89)
Diagnosis of diabetes			
<7.2 mmol/L	**2.60 (1.28, 5.28)**		**2.13 (1.04, 4.37)**
≥7.2 mmol/L	**3.08 (2.00, 4.77)**		1.34 (0.73, 2.48)
HbA1c			
No diagnosis of diabetes			
HbA1c <5.7%	1 (reference)	1 (reference)	
HbA1c 5.7-6.4%	**1.49 (1.06, 2.09)**	**1.47 (1.05, 2.07)**	
HbA1c ≥6.5%	**3.19 (1.91, 5.34)**	**3.03 (1.73, 5.30)**	
Diagnosis of diabetes			
HbA1c <7.0%	1.85 (0.96, 3.58)	1.80 (0.92, 3.51)	
HbA1c ≥7.0%	**4.72 (3.12, 7.16)**	**4.23 (2.28, 7.84)**	

Models are the same as Table 2.

Web Table 3. Adjusted HRs (95% CIs) for peripheral artery disease without critical limb ischemia by categories of fructosamine, glycated albumin, and 1,5-AG (N = 10,310) (lowest level as reference [highest for 1,5-AG])

	PAD without CLI n=239		
	Model 1	Model 2a	Model 2b
Fructosamine			
No diagnosis of diabetes			
<77th Percentile (<241.5 µmol/L)	1 (reference)	1 (reference)	1 (reference)
77th-95th Percentile (241.5 - 270.0 µmol/L)	0.86 (0.58, 1.29)	0.83 (0.56, 1.25)	0.82 (0.55, 1.23)
≥96th Percentile (≥270.1 µmol/L)	1.44 (0.79, 2.64)	1.12 (0.58, 2.16)	0.95 (0.49, 1.84)
Diagnosis of diabetes			
<32nd Percentile (<275.3 µmol/L)	**2.03 (1.14, 3.62)**	1.79 (0.99, 3.23)	1.62 (0.90, 2.92)
≥32nd Percentile (≥275.3 µmol/L)	**3.20 (2.12, 4.83)**	1.87 (0.99, 3.55)	1.28 (0.67, 2.43)
Glycated albumin			
No diagnosis of diabetes			
<77th Percentile (<13.6%)	1 (reference)	1 (reference)	1 (reference)
77th-95th Percentile (13.6 - 15.5%)	1.16 (0.78, 1.74)	1.14 (0.76, 1.70)	1.09 (0.73, 1.64)
≥96th Percentile (≥15.6%)	1.78 (0.98, 3.24)	1.45 (0.75, 2.80)	1.15 (0.59, 2.25)
Diagnosis of diabetes			
<32nd Percentile (<16.4%)	**1.91 (1.05, 3.47)**	1.74 (0.95, 3.20)	1.58 (0.86, 2.91)
≥32nd Percentile (≥16.4%)	**3.63 (2.42, 5.45)**	**2.45 (1.30, 4.60)**	1.59 (0.83, 3.05)
1,5-AG			
No diagnosis of diabetes			
>23rd Percentile (>14.6 ug/ml)	1 (reference)	1 (reference)	1 (reference)
5th-23rd Percentile (7.9 - 14.6 ug/ml)	1.00 (0.68, 1.47)	0.99 (0.68, 1.45)	0.98 (0.67, 1.44)
≤4th Percentile (≤7.8 ug/ml)	1.62 (0.89, 2.92)	1.41 (0.76, 2.64)	1.21 (0.64, 2.29)
Diagnosis of diabetes			
>68th Percentile (>9.7 ug/ml)	1.54 (0.80, 2.95)	1.40 (0.72, 2.72)	1.28 (0.66, 2.49)
≤68th Percentile (≤9.7 ug/ml)	**3.72 (2.51, 5.53)**	**2.67 (1.48, 4.81)**	**1.85 (1.00, 3.39)**

Models are the same as Table 2.

Web Table 4. Adjusted HRs (95% CIs) for peripheral artery disease without critical limb ischemia by categories of fructosamine, glycated albumin, and 1,5-AG (N = 10,310) (lowest risk group as reference)

	PAD without CLI n=239		
	Model 1	Model 2a	Model 2b
Fructosamine			
No diagnosis of diabetes			
<77th Percentile (<241.5 µmol/L)	1.16 (0.78, 1.73)	1.20 (0.80, 1.79)	1.22 (0.81, 1.82)
77th-95th Percentile (241.5 - 270.0 µmol/L)	1 (reference)	1 (reference)	1 (reference)
≥96th Percentile (≥270.1 µmol/L)	1.67 (0.85, 3.28)	1.35 (0.66, 2.74)	1.16 (0.56, 2.37)
Diagnosis of diabetes			
<32nd Percentile (<275.3 µmol/L)	**2.35 (1.21, 4.57)**	**2.15 (1.10, 4.21)**	**1.97 (1.00, 3.85)**
≥32nd Percentile (≥275.3 µmol/L)	**3.70 (2.22, 6.17)**	**2.25 (1.13, 4.46)**	1.55 (0.78, 3.10)
Glycated albumin			
No diagnosis of diabetes			
<77th Percentile (<13.6%)	1 (reference)	1 (reference)	1 (reference)
77th-95th Percentile (13.6 - 15.5%)	1.16 (0.78, 1.74)	1.14 (0.76, 1.70)	1.09 (0.73, 1.64)
≥96th Percentile (≥15.6%)	1.78 (0.98, 3.24)	1.45 (0.75, 2.80)	1.15 (0.59, 2.25)
Diagnosis of diabetes			
<32nd Percentile (<16.4%)	**1.91 (1.05, 3.47)**	1.74 (0.95, 3.20)	1.58 (0.86, 2.91)
≥32nd Percentile (≥16.4%)	**3.63 (2.42, 5.45)**	**2.45 (1.30, 4.60)**	1.59 (0.83, 3.05)
1,5-AG			
No diagnosis of diabetes			
>23rd Percentile (>14.6 ug/ml)	1.00 (0.68, 1.46)	1.01 (0.69, 1.48)	1.02 (0.69, 1.49)
5th-23rd Percentile (7.9 - 14.6 ug/ml)	1 (reference)	1 (reference)	1 (reference)
≤4th Percentile (≤7.8 ug/ml)	1.61 (0.83, 3.14)	1.42 (0.71, 2.84)	1.23 (0.61, 2.49)
Diagnosis of diabetes			
>68th Percentile (>9.7 ug/ml)	1.53 (0.75, 3.15)	1.41 (0.68, 2.92)	1.30 (0.63, 2.70)
≤68th Percentile (≤9.7 ug/ml)	**3.72 (2.26, 6.11)**	**2.69 (1.40, 5.17)**	1.88 (0.96, 3.67)

Models are the same as Table 2.

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Curriculum Vitae

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EDUCATION

Master of Science in Epidemiology Expected May 2017
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Certificate in Pharmacoepidemiology and Drug Safety Expected May 2017
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Certified in Public Health Mar. 2017
National Board of Public Health Examiners, Washington, D.C.

Bachelor of Medicine Jul. 2015
Peking University School of Medicine, Beijing, China

- First Prize Scholarship (2014), Merit Student (2011, 2013, 2014), National Scholarship (2012, 2013), Pacemaker to Merit Student (2012)

TECHNICAL SKILLS

- **Computer Skills:** MS Office Word, Excel, PowerPoint, Tableau, ArcGIS, Endnote, RevMan
- **Statistical Programming**: SAS, STATA, SPSS; Familiar with R
- **Data Management**: MySQL, REDCap, Access, Google Spreadsheet
- **Certificate:** SAS Certified Base Programmer for SAS 9, SAS Certified Advanced Programmer for SAS 9, HIPAA (patient privacy), CITI (human subjects research)

DATA ANALYSIS EXPERIENCE

Research Assistant Jan. 2016 to Present
Johns Hopkins Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD

- Developing analysis plans, conducting quantitative cross-sectional and longitudinal data analysis on several projects using Stata
- Performing literature review, drafting proposal and manuscript

Epi Scholar Summer Intern May 2016 to Aug. 2016
New York City Department of Health and Mental Hygiene, New York, NY

- Performed literature review and synthesized relevant studies
- Conducted analysis and interpretation on the prevalence and treatment of high cholesterol in SAS using data from the New York City Health and Nutrition Examination Survey
- Presented the findings on Epi Scholar Program final presentation and completed a manuscript to submit for publication

Research Assistant Oct. 2013 to Sept. 2014

Peking University Fourth Teaching Hospital, Beijing, China

- Participated in a comparative effectiveness study of thrombus aspiration devices: extracted data from electronic medical records, collected and managed data in spreadsheets
- Reviewed literature and extracted data for a systematic review and meta-analysis of the effectiveness of thrombectomy

Leading Researcher Jul. 2013 to Aug. 2014

Peking University Health Science Center, Beijing, China

Project title: *The Evaluation of Objective Structured Clinical Examination (OSCE) Based on Medical Students' Perspective*

- Designed questionnaire, conducted key informant interviews, administered survey of 450 medical students, entered data, monitored data quality, and analyzed data
- Resulted in a report to the Education Office of Peking University

Research Assistant Nov. 2012 to May 2013

Peking University Third Hospital, Beijing, China

- Assisted in Nationally Representative Survey on Chinese Adult Pulmonary Function
- Performed physical examination and pulmonary function test, administrated questionnaires, entered and managed data

CLINICAL EXPERIENCE

Intern Doctor Aug. 2013 to Jul. 2015

Peking University Fourth Teaching Hospital, Beijing, China

- Systematically learned clinical knowledge in Internal Medicine, Surgical Medicine, Obstetrics and Gynecology, Pharmacology, etc.
- Clinical rotation: in charge of patients, writing case records, assisting surgery

PUBLICATIONS/PRESENTATIONS

- **Ning Ding**, Kunihiro Matsushita, et al. "Glycemic Markers and Risk of Peripheral Artery Disease: The Atherosclerosis Risk in Communities (ARIC) Study". *Presented at the American Heart Association Epidemiology and Prevention Scientific Sessions, 2017*.

- **Ning Ding**, Sharon Perlman, Claudia Chernov, Rania Kanchi, Lorna Thorp, Winfred Wu. The Prevalence and Treatment of High Cholesterol in New York City 2013-2014. *(In preparation)*

- Yu-Qing Ouyang, **Ning Ding**, Yun Bai, Xuan Fang, Jie-wei Wang, Yan Xu. 2015. The Evaluation of Objective Structured Clinical Examination (OSCE) Based on Medical Students' Perspective. *Chinese Journal of Medical Education. vol. 35*, 2015.8: 634-637.

- **Ning Ding**, Yu-Qing Ouyang, Guo-Gang Xing. 2015.The Role of Corticotropin-Releasing Factor and its Receptors in Pain and Related Negative Emotions. *Chinese Journal of Pain Medicine. vol. 21,* 2015.6: 449-453.

- **Ning Ding**, Yi-nan Fu, Yan Tang, Feng Li, Jun-min Tang. 2014. Immunohistochemical Quantity Analysis of CD3, CD4, CD8 in Human Normal Cervical Tissue. *Medical Journal of Chinese People's Health*, *vol. 26,* 2014.3: 1-3.